REMARKS

STATUS OF THE CLAIMS

Following entry of this Amendment, claims 12, 14, 31, 33-34, 36-37, 39, 41-42, and 44-50 will be pending. Please cancel claims 32, 35, and 38, 40, and 43. Please add new claims 45-50. Claims 31, 33-34, 36-37, 42, and 44 have been amended. Claims 46-50 recite human M-CSF. Support for claims 46-50 can be found in the specification on page 17, lines 19-21.

I. OBJECTION TO THE TITLE OF THE INVENTION

The Examiner objected to the title of the invention as allegedly being not descriptive.

Applicants have amended the title of the invention to recite "Methods of Treating Inflammation Using Antibodies to M-CSF." Applicants maintain that the amended title is sufficiently descriptive of the claimed invention. Applicants request that this objection be withdrawn.

II. OBJECTION TO THE FIGURES UNDER 37 CFR §§ 1.84(g) AND 1.85

The Examiner has objected to Figures 1, 3, 5, 9, 11, and 15-21 under 37 CFR §§ 1.84(g) and 1.85.

Applicant has provided attached sheets that include changes to Figures 1, 3, 5, 9, 11, and 15-21. These sheets, which include Figures 2, 4, 6-8, 10, and 12-14, replace the original sheets including Figures 1, 3, 5, 9, 11, and 15-21. Applicants maintain that current set of Figures comply with 37 CFR §§ 1.84(g) and 1.85. Applicants request that this objection be withdrawn.

III. OBJECTION TO THE DEPENDENCIES OF CLAIMS 32, 35 AND 36.

The Examiner has objected to claims 32, 35 and 36 as being dependent upon themselves.

Applicants have canceled claims 32 and 35. Claim 36 has been amended to depend from claim 34. Applicants request that this objection be withdrawn.

IV. REJECTION UNDER THE SECOND PARAGRAPH OF 35 U.S.C. § 112

The Examiner has rejected claims 38, 39 and 40-44 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for the lack of antecedent bases for terms recited in the rejected claims. Each of these rejections will be addressed in turn.

A). The Examiner rejected claim 40 because base claim 14 and base claim 12 do not recite "antagonist" and "mCSF".

Applicants have cancelled claim 40. Applicants respectfully request that this rejection be withdrawn.

B). The Examiner rejected claim 41 because base claim 14 and base claim 12 do not recite "antibody".

Applicants have amended claim 12 to recite the term "antibody." Claim 41 depends from claim 14, which depends from claim 12. Applicants maintain that claim 41 presently complies with the definiteness requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that this rejection be withdrawn.

C). The Examiner rejected claim 43 because base claim 36 does not recite "antagonist".

Applicants have cancelled claim 43. Applicants respectfully request that this rejection be withdrawn.

D). The Examiner rejected claim 44 because base claim 37 and base claim 31 do not recite "antibody".

Applicants have amended claim 44 to depend from claim 33. Claim 33 recites the term "antibody." Applicants respectfully request that this rejection be withdrawn.

E). The Examiner rejected claim 38 because base claim 36 does not recite "antagonist".

Applicants have cancelled claim 38. Applicants respectfully request that this rejection be withdrawn.

F). The Examiner rejected claim 39 because base claim 37 and base claim 31 do not recite "antibody".

Applicants have amended claims 31 and 37 to recite the term "antibody." Applicants maintain that claim 39 presently complies with the definiteness requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that this rejection be withdrawn.

G). The Examiner rejected claim 42 as being indefinite and ambiguous in the recitation of "...treating asthma by administrating mCSF antagonist to treat psoriasis".

Applicants have amended claim 42 to delete "psoriasis" and insert therefor "asthma." Applicants maintain that claim 42 presently complies with the definiteness requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request that this rejection be withdrawn.

V. REJECTION UNDER FIRST PARAGRAPH OF 35 U.S.C. §112

The Examiner has rejected claims 12, 14, 31- 44 under 35 U.S.C. 112, first paragraph, as allegedly not being enabled for 1) a method of treating inflammation, such as sepsis, comprising administering to a mammal a therapeutically effective amount of any inhibitor of a CSF, claimed in Claims 12 and 14, or 2) a method of treating inflammation, such as psoriasis or asthma, comprising administering to a mammal a therapeutically effective amount of any inhibitor of a m-CSF, such as antibody, claimed in Claims 31, 32, 37 and 42 or 3) a method of treating rheumatoid arthritis in a mammal comprising administering any mCSF antagonist, such as antibody, claimed in Claims 34 and 35.

Applicants respectfully maintain that the claims, as amended, are sufficiently enabled under 35 USC § 112, first paragraph.

The Examiner stated, "it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of any antagonist or any inhibitor of CSF or mCSF, broadly encompassed by the claimed invention." Applicants have amended claims 12, and 31 to delete "inhibitor of a CSF" or "m-CSF inhibitor," respectively and insert therefor "antibody to a M-CSF." Applicants have also amended claims 34, 37, and 42 to delete "mCSF antagonist" and insert therefor "antibody to a M-CSF." Similarly, new claims 46-50 are directed towards methods of treatment using an antibody to a human M-CSF.

Applicants also maintain that specification permits one of ordinary skill in the art to practice the invention as currently claimed. The USPTO's guidelines on written description are instructive as to the level of skill and predictability of raising antibodies to a known antigen in Example 16 in the Synopsis of Application of Written Description Guidelines:

> It is also well known that antibodies can be made against virtually any protein. ... The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. This is a mature technology where the level of skill is high and advanced. (Guidelines page 59-60) (emphasis added).

Accordingly, Applicants maintain that given the nature of antibody technology and that the level of skill is high and advanced, one of skill in the art can practice the claimed methods of using M-CSF antibodies without undue experimentation.

The Examiner has also averred that it is not clear that one of skill could predict the efficacy of the claimed methods and cited Van Noort et al. *International Review of Cytology*, 1998, 178: 127-204. Applicants respectfully respond that complete predictability of a method of treatment is not the standard for enablement. Also, the Examiner has directed the Applicants to Table III for

support for his allegation. Table III is a listing of animal models of infectious disease models and autoimmune diseases. Table III does not detail any lack of correlation between in vitro and in vivo results using these models. In addition, that some experimentation may be necessary to practice the claimed invention or to test the claimed antibodies in an animal model is insufficient to reject the claims as not being enabled.

The Examiner also cited Campbell et al. (*J. of Immunol.* 1998, 161: 3639-3644) as disclosing that there are limitations to treating inflammation with inhibitors of a CSF or receptor antagonists of the cytokines in an animal model of arthritis - CIA, such as: 1) the inhibitors of CSF, including monoclonal antibody may not be accessible to the site of the action; 2) there may be reduced efficacy of the neutralizing antibody due to an immune response to this foreign protein.

Applicants respectfully point out that neutralizing antibodies for the cytokine TNFα have been shown to ameliorate arthritis in a CIA and in humans (Williams et al. (1992) *Proc. Nat'l. Acad. U.S.A.* 9784-9788; and Feldman et al. (1998) *Transplantation Proceedings* 30: 4126-4127, copies of which have been submitted in the accompanying Supplemental IDS). For example, Williams et al. disclosed on page 9784 that antibodies to TNFα caused a "significant reduction in the clinical and histopathological severity of collagen-induced arthritis whether carried out before or after the onset of clinical disease." Further, Williams et al. state that cytokine specific immunotherapy may be a valid alternative to cell-depleting reagents such as anti-CD4 antibodies (page 9787). Moreover, Feldman et al., disclose that a marketed anti-TNFα antibody (REMICADE®) is useful for the treatment of rheumatoid arthritis and Crohn's disease (see e.g., page 4126). The references demonstrate that an anti-cytokine antibody is efficacious in treating CIA in animals and can be used to treat rheumatoid arthritis in humans.

The Examiner has further alleged that the "specification does not provide sufficient teaching as to how it can be assessed that treating inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis was achieved after the administration of a therapeutically effective amount of inhibitor of a CSF or inhibitor of

mCSF." Applicants point out that it is well within the purview of the ordinary skilled scientist or clinician to determine a therapeutically effective amount of an anti-M-CSF antibody for a subject and to determine if the subject is benefiting from the therapy. The specification does not need to disclose for enablement that which is known to one of skill in the art.

In conclusion, Applicants maintain that the specification enables one of skill in the art to practice the claimed invention without undue experimentation. Accordingly, Applicants respectfully request that the enablement rejection under 35 U.S.C. § 112 be withdrawn.

VI. REJECTION UNDER FIRST PARAGRAPH OF 35 U.S.C. §112 – WRITTEN DESCRIPTION

The Examiner has rejected claims 12, 14, 31- 44 under 35 U.S.C. 112, first paragraph, for lacking an adequate written description of: 1) a method of treating inflammation, comprising administering to a mammal a therapeutically effective amount of any inhibitor of a CSF, claimed in Claim 12, or 2) a method of treating inflammation, comprising administering to a mammal a therapeutically effective amount of any inhibitor of a m-CSF, claimed in Claim 31, or 3) a method of treating rheumatoid arthritis in a mammal comprising administering any mCSF antagonist, claimed in Claim 34. The Examiner directed the Applicants to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099- 1111, Friday January 5, 2001.

Applicants respectfully maintain that the claims, as amended, are sufficiently described under 35 USC § 112, first paragraph. The Applicants respectfully point out that the claims have been amended to relate to methods of treating diseases by administering antibodies to a M-CSF or antibodies to a human M-CSF.

The applicable legal standard for determining compliance with the written description requirement of 35 USC § 112, first paragraph include the PTO's own guidelines (http://www.uspto.gov/web/patents/guides.htm; "Revised Interim Written

Description Guidelines Training Materials"). *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1325, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002).

The written description requirement is met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324, 63 U.S.P.Q.2d at 1613, citing Guidelines, 66 Fed. Reg. at 1106. The *Enzo* court went on to state that the PTO would find written description compliance for a claim to:

> an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines"). *Id.*

The example the *Enzo* court refers to is Example 16 of the Application of Guidelines. In Example 16, the claims are drawn to "[a]n isolated antibody capable of binding to antigen X." Application of Guidelines at 59. In Example 16, the specification disclosed that:

> antigen X has been isolated and is useful for detection of HIV infections. The specification contemplates but does not teach in an example antibodies which specifically bind to antigen X and asserts that these antibodies can be used in immunoassays to detect HIV. The general knowledge in the art is such that antibodies are structurally well characterized. It is well known that all mammals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA and IgE. Antibodies contain an effector portion which is the constant region and a variable region that contains the antigen binding sites in the form of complementarity determining regions and the framework regions. The sequences of constant regions as well as the variable regions subgroups (framework regions) from a variety of species are known and published in the art. *Id.*

The analysis section of the Example goes on to state that:

> The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. This is a mature technology where the level of skill is high and advanced. The claim is directed to any antibody which is capable of binding to antigen X. A search of the prior art indicates that antigen X is novel and unobvious. Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X. *Id.* at 59-60.

The Guidelines concluded that Example 16 compiles with the written description requirement of under 35 USC § 112 first paragraph. Thus, under the Guidelines and applicable Federal Circuit jurisprudence, the written description requirement would be met for the present claims if the functional characteristic of an antibody that bound to M-CSF were coupled to a sufficient correlation between that function and a sufficiently known or disclosed structure. *See Enzo*, 296 F.3d 1324-5, 63 U.S.P.Q.2d at 1613. M-CSF polypeptides (e.g., human M-CSF) are polypeptide antigens. Thus, the "spectrum of antibodies which bind to" an M-CSF are implicitly disclosed in the specification. Moreover, the specification discloses that inhibitors of the present invention include antibodies directed to M-CSF (see e.g., page 15, lines 9-12) and that they have therapeutic applications (see e.g., page 18, lines 5-11). Accordingly, the presently claimed methods of treatment that relate to the use of M-CSF antibodies are sufficiently described in the specification. Therefore, Applicants respectfully request that the written description rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at 734-622-2095.

Respectfully submitted,

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